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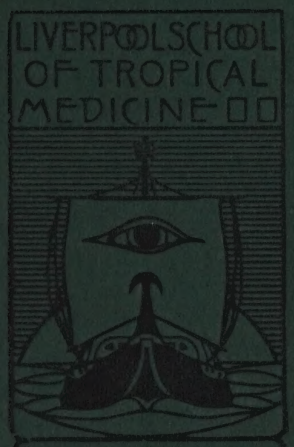

ANNALS

Edited by
RONALD ROSS
in collaboration
with
J. W. W. Stephens
R. Newstead
J. L. Todd
H. W. Thomas
Anton Breinl
Sir Rubert Boyce

A Case of Sleeping Sickness Studied by Precise Enumerative Methods: Further Observations

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Major RONALD ROSS, F.R.S.,
AND
DAVID THOMSON, M.B., Ch.B., D.P.H.

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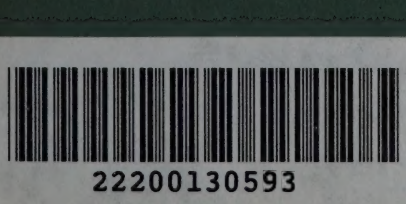

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A CASE OF SLEEPING SICKNESS STUDIED BY PRECISE ENUMERATIVE METHODS: FURTHER OBSERVATIONS

BY

MAJOR RONALD ROSS, F.R.S.,

AND

DAVID THOMSON, M.B., CH.B., D.P.H.

(*Received for publication* 15 *October*, 1910)*

I. INTRODUCTION

In a previous paper† by us, we recorded our observations on this case during two and a half months, and described particularly the regular periodical rises in the numbers of trypanosomes disclosed in the patient's peripheral blood by methodical daily countings extending over that period. Our technique has been detailed in another paper by us on 'Enumerative Studies on Malarial Fever.'‡ We now record our further observations on the case during two more months—until the patient's death. A chart and a table giving daily details of the observations are attached; and accompanying papers by Drs. H. B. Fantham and J. G. Thomson record studies on animals and on the parasites themselves. We must refer also to a recent communication by Drs. J. W. W. Stephens and Fantham§ suggesting that the species found in this case may not be identical with *T. gambiense*.

The patient, a strong young Englishman, age 26, weight 154 lbs., was infected in N.E. Rhodesia near the River Luangwa in September, 1909. The trypanosomes were found in his blood in Africa on November 17.

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* Reprinted from Proc. Roy. Soc., B, Vol. LXXXIII, p. 187.

† Proc. Roy. Soc., July 21, 1910, B, 557.

‡ Ann. Trop. Med. and Parasit., Vol. IV., No. 3.

§ *Ibid.*

He was admitted into the Royal Southern Hospital on December 4. Daily estimation of the number of trypanosomes per cubic millimetre of his blood was commenced on February 16, and continued till his death on June 29, a period of 134 days. During that period we never failed to find trypanosomes. The history of the case from February 16 is recorded graphically on the chart.

The patient had glandular swellings and ill-defined erythematous rashes on his legs at various intervals. On April 20 he had a severe attack of vomiting which continued for four days; in consequence he lost 10 lbs. in weight and was never again so well. He remained in bed onwards till his death. He became progressively more drowsy, with intervals of more or less comparative brightness. His memory and mental powers failed steadily. On May 7 he developed a marked neuritis due to the atoxyl, and every dose seemed to aggravate the neuro-retinitis produced by the previous administration of this drug. His eyes were examined weekly by Dr. Hamilton, oculist to the hospital.

On May 10 both legs became markedly oedematous and remained so till his death. On May 13 he became much worse and developed paralysis of his sphincters. He seemed about to die, but on May 20 a sudden remarkable improvement took place. Soon, however, he again commenced to grow steadily worse.

On June 25 he developed pleurisy and pneumonia. He died on June 29.

Post mortem.—Performed twenty-two hours after death:—

Brain.—Membranes thickened and white. Vessels congested. Cerebrospinal fluid increased.

Left lung.—Broncho-pneumonia.

Left pleural cavity.—Contained one pint of yellow pussy fluid.

Spleen.—Soft and much enlarged; weight, 33 ozs.

Liver.—Enlarged; weight, 6 lbs.

Blood.—No trypanosomes could be found. Leucocytes, 17,000 per cubic millimetre. Polymorph excess.

Smears of bone marrow, spleen, kidney, mesenteric glands, and cerebrospinal fluid, all showed large numbers of small and large mononuclear cells, but no trypanosomes could be detected.

II. CONTINUANCE OF THE PERIODICAL CYCLE

The cycle recorded by us till April 30 in our previous paper continued till his death. From February 22 till June 25 there occurred nineteen rises in the numbers of trypanosomes in his peripheral blood. This gives an average of six and a half days between the heights of each rise:

The shortest period between two successive heights is four days, as recorded between April 18 and 22, and again between June 3 and 7. This exceptionally short interval was due, we think, to artificial means, as we shall explain later under vaccine treatment. The longest period recorded between two successive heights is eight days, while the usual period between the heights seems to be seven days. It will be observed that the rise and fall is sudden, and that the height is not maintained.

While the number of the parasites was increasing rapidly, we observed many forms with double nuclei and blepharoplasts (dividing forms). During the interval between the rises, few of these forms were present. This would seem to indicate that the sudden rise is due to an active multiplication of the parasites.

On April 28 the numbers increased from 200 to 1,536 in twenty-four hours, and on June 19 they increased from 100 to 1,500 in twenty-four hours, suggesting that in our patient they were capable of dividing and sub-dividing three to four times in twenty-four hours.

The natural fall is even more sudden than the rise. On April 29 the parasites fell from 1,536 to 100 per cubic millimetre of blood in twenty-four hours.

Except on April 5 and 6 only one observation was made daily, so that obviously we may have missed the highest points reached in the various rises. The low levels were, as a rule, maintained for three or four days, forming **U**-shaped bends as recorded in the chart. The lowest number recorded was 8 per cubic millimetre of blood, while the highest reached 1,536 per cubic millimetre of blood.

It is worthy of note that there is a tendency for a high rise to be followed by a low one. This is not without exception, but the three highest rises recorded were followed by the three lowest rises.

III. CORRELATION BETWEEN THE CYCLE AND THE AMOUNT OF FEVER

From the chart one can observe that almost invariably the temperature tends to be higher during the height of the cycle, and that between the rises the temperature keeps lower.

In the table average daily temperatures are recorded. These figures were obtained by taking the average of the four-hourly temperatures observed during the twenty-four hours of each day. We think that this figure gives a fair representation of the amount of fever for the day, and in this table it may be noted that the average daily temperature rises coincidently with the increase of trypanosomes and falls with their fall.

IV. OTHER CLINICAL OBSERVATIONS AND CORRELATIONS WITH THE CYCLE

The pulse rate ranged all through this case from 90 to 120 per minute. During the height of the cycle it tended to increase coincidently with the increased amount of fever. The respiration rate ranged from 20 to 28 per minute, tending also to increase with the rise of the trypanosomes.

With regard to the bowels there is little to note. Their action was easily regulated with small doses of cascara. It was very noticeable that the patient was more drowsy, and tended to have headaches, during the commencement of the cyclical rise, but these symptoms abated at the extreme height and during the subsequent fall of trypanosomes.

The lymphatic glands in the neck, axilla, groin, and poplitcal space were more or less always swollen, but this condition was greatly aggravated at intervals, accompanied with marked tenderness, though only sometimes was this coincident with a trypanosome increase.

The urine throughout remained clear, usually slightly acid and without deposits. The specific gravity ranged from 1010 to 1026.

On March 15 he had a diffuse ill-defined erythematous rash over his left leg, occurring just before the height of a trypanosome increase.

V. CORRELATION BETWEEN THE TRYPANOSOME CYCLE AND THE BEHAVIOUR OF THE LEUCOCYTES

Previous to April 23 we made several leucocyte counts with the Thoma-Zeiss apparatus, but were unable to find anything definite. It was only when we made counts daily at the same hour that we were able to find a definite leucocyte change corresponding to the parasitic cycle.

We counted the leucocytes by means of the thick film as referred to in our paper on malaria, and were astonished at the remarkable variations. We found no such variations by our method in normal persons. Simultaneous examination of thin blood films also showed that a remarkable leucocytic variation did take place, corresponding to each rise of trypanosomes.

Daily differential counts were also made in thin films stained with Giemsa, in which we distinguished only between mononuclears and the so-called polymorphonuclears. In these we never counted less than from 300 to 500 leucocytes to ensure greater accuracy. We thus estimated daily the total leucocytes and the total numbers of polymorphs and mononuclears per cubic millimetre of blood, as shown in the chart and table.

From April 23 till May 20 it is clearly seen that coincident with each rise in the number of trypanosomes there is a marked increase in the total leucocytes, and this increase is due more to mononuclears than to polymorphonuclears.

When the trypanosomes begin to increase in number the leucocytes increase also, more especially the mononuclears. When the trypanosomes have reached their height there may be a fall in the number of leucocytes, but this is followed by a still higher rise during the fall of the trypanosomes. The leucocytes would seem to reach their highest numbers on about the third day after the height of the parasitic cycle. They then decrease rapidly for about three days to normal or much lower. When this occurs the trypanosomes again commence to multiply, and the leucocytes again increase also, so that we have both a parasitic and a corresponding leucocytic cycle.

We did not attempt to differentiate between large mononuclears and lymphocytes, but it seemed to us that both took part in the total mononuclear increase. We further observed that during and

immediately after the parasitic fall the large mononuclears were filled with vacuoles and a reddish *débris* (stained Giemsa). Many of these vacuolated mononuclear cells were of great size (30 to 40 microns in diameter). We are inclined to think that this vacuolation with reddish stained *débris* may be an indication of the ingestion of trypanosomes, although we have never observed any definite trypanosome structure within them.

F. W. Andrewes, in the Croonian Lectures,* points out that an intravenous injection of bacteria causes a temporary diminution in leucocytes, followed by a marked increase, this fall and rise being chiefly due to the so-called polymorphonuclears, the mononuclears taking little part in the phenomenon. In this disease, as in malaria, it would appear that there is a diminution followed by an increase, chiefly of the mononuclears. This tends to suggest that the polymorphonuclear leucocytes react chiefly to bacterial infections, while the mononuclears would seem to react chiefly to protozoal blood infections (D. T).

It is interesting to note that on May 20 there was a very marked mononuclear increase, coincident with a fall of trypanosomes, and accompanied by a remarkable improvement in the clinical condition of the patient; and again on June 24 the mononuclear excess changed into a very marked polymorph excess. This was coincident with the onset of pleurisy and pneumonia, from which the patient died.

In connection with the leucocyte cycle, the highest numbers recorded were 50,000 per cubic millimetre of blood, whereas the lowest was 2,800 per cubic millimetre of blood. In the latter part of the chart the leucocytic graph is altered by the injection of leucocytic extract, and by the development of an abscess and pneumonia.

The following quotation from the 'Sleeping Sickness Bulletin,' 1908, No. I, p. 5, is of interest:—'Dr. W. Thomas found that 'after an injection of atoxyl a change in the parasites became 'noticeable between the fourth and the fifth hour. They became 'sluggish and much altered in appearance, and at the same time 'there was a noticeable increase in the leucocytes. About the seventh 'hour there was a great diminution in the number of trypanosomes,

* Lancet, July, 1910

'and a coincident increase in the leucocytes, notably the phagocytes. 'At the eighteenth hour parasites were absent and could not be 'found, even after blood centrifugalisation. Instances of 'phagocytosis were observed on three occasions.'

Thomas and Breinl tried the effect of hyperleucocytic agents without good effects, but remark: 'It is quite evident that the 'leucocytes play a rôle in the decrease of parasites.'

We think that it is possible that on some occasions, at least, Thomas may have happened to give atoxyl at the time when the leucocytes were increasing and the parasites were diminishing, as we have shown to occur naturally.

VI. THE HAEMOGLOBIN AND RED CELLS

During the course of the disease, from February till the patient's death in June, the haemoglobin percentage fell more or less steadily from 85 to 70 per cent. We could not detect any variation in the amount of haemoglobin corresponding to the parasitic cycle.

The number of red cells was deficient (3,800,000 in March; 2,800,000 in June). Their numbers were not estimated frequently.

VII. THE EFFECTS OF TREATMENT BY VARIOUS DRUGS

The crucial test of a curative treatment in this disease would naturally be the effect of the treatment on the numbers of parasites, especially in our case, where the numbers were estimated daily.

In testing the value of various therapeutic agents, we have therefore taken the graph of the number of parasites as the indicator of the efficacy of that agent. We would like also to point out that in estimating the effect of treatment by this method, the blood must be examined every day, otherwise the effects recorded might be erroneous. If a drug be given at the height of a parasitic rise, and the blood examined next day or a few days later, the number of parasites would naturally be much less; to conclude from this that the drug has caused this diminution might be quite erroneous. It is obvious that no conclusion should be drawn until the numbers have been estimated daily for several weeks.

We think it may be possible that a drug such as atoxyl may by chance have been given, sometimes, just as the parasites were

naturally about to fall, and the rapid diminution attributed to the drug.

It has been stated that atoxyl did not always cause a disappearance of the parasites, but that sometimes instead they even increased in numbers; and further, that it seemed to have a more marked trypanocidal action when the parasites were very numerous.

These statements can be understood in the light of the natural cycle.

Again, if the trypanosomes increase in number immediately after the administration of a drug, one cannot at once conclude that this drug is of no value as a trypanocide.

The Effect of Atoxyl

From February 16 till April 5 atoxyl was not given, on account of its injurious effect on the patient's eyes. On April 5 we, however, injected a dose of four grains at the commencement of a natural rise. The blood was examined every two hours afterwards and showed that the trypanosomes were increasing in numbers. Twenty-four hours later there was a further marked increase. Next day again, as we would have expected to occur naturally, there was a decided diminution in their number.

On May 2 atoxyl was again given, though it was found that every dose aggravated the eye condition. From May 2 till June 20, thirty-two grains of atoxyl in all were administered at intervals, as noted on the chart. On comparing the graph where no atoxyl was given, and where it was administered, no very appreciable difference in the number of trypanosomes can be detected. We cannot, however, conclude that the atoxyl has no trypanocidal effect, as had it not been given the trypanosomes may possibly have been much more numerous during the latter than in the earlier part of the chart; and further, this particular strain of trypanosomes seems to have been very virulent.

Our doses of atoxyl in any case were rather small. It would appear to us, however, that atoxyl cannot be considered a specific in human trypanosomiasis, as quinine is in malaria. In our cases of malaria quinine never failed to diminish, markedly, the number of asexual parasites. Moreover, atoxyl compared with quinine is a dangerous drug.

Quinine and Methylene Blue Treatment

Quinine 30 grains daily, combined with methylene blue, 12 grains daily, was administered by the mouth from February 21 till March 9, and again at other intervals as noted on the chart. No marked trypanocidal effect can be noticed.

During treatment with these drugs, however, as also with atoxyl, the patient's face, which had before been puffy and oedematous, especially about the eyelids, became more firm and clear cut. The eyelids became again oedematous soon after these drugs were withheld. It would seem, therefore, that quinine and methylene blue, as well as atoxyl, had some beneficial effect clinically. The following drugs were also given without apparent results:—

(*a*) *Trypsin and Amylopsin Injections.*—20 min. of each daily.

(*b*) *Succinamide of Mercury Injection.*—One-fifth grain almost daily.

(*c*) *Izal Oil.*—8 min. daily, by mouth.

(*d*) *Trypan Red.*—By the mouth in doses of 0·5 grain, 1 grain, and 1 grain respectively on three successive days. No albuminuria resulted, but the drug was stopped on account of the development of severe vomiting.

(*e*) *Potassium Iodide.*—30 grains daily, by mouth.

We beg to apologise for complicating the case with so many treatments, but owing to the unsuitability of atoxyl in the patient other treatment was a clinical necessity.

VIII. EFFECT OF TRYPANOSOME 'VACCINES

On April 19 we commenced to give our patient subcutaneous injections of so-called vaccine. This vaccine was obtained from the blood of a rat inoculated from our patient. The rat was killed when the parasites were extremely numerous (500,000 per cubic millimetre of blood). The blood was then drawn from its heart aseptically, and mixed with an equal volume of normal saline. The red cells were allowed to settle, and the supernatant fluid pipetted off. This latter contained most of the trypanosomes and the number per cubic millimetre was estimated by the thick film method. It was then sterilised by heating to 55° C. for half-an-hour, and by adding trikresol so that it contained 0·2 per cent.

The later vaccines which we commenced to use from May 17 were simply the blood of rats, taken when the trypanosomes were very numerous. They consisted of dead trypanosomes, red cells, leucocytes, and serum. The injection of these vaccines produced no local reaction, even in doses of 100,000,000 trypanosomes; nor were we able to detect any definite temperature reaction.

We are inclined to think that the chief result of these injections of dead trypanosomes was a stimulation of the reproductive powers of the living trypanosomes. This point, however, requires further elucidation. We found that after an injection of our vaccine, the next trypanosome rise usually occurred before it was naturally due.

On April 9, 9,000,000 dead trypanosomes were injected; the next trypanosome rise reached its height on the seventh day. 20,000,000 were again injected on April 13, and the following rise was completed on the sixth day. 40,000,000 were then injected and the next rise was completed on the fifth day.

The patient's trypanosomes, also, which were rising to successively smaller heights, continued to diminish further in number, after two more injections of 10,000,000 dead trypanosomes on April 23 and 25. On April 28, however, an injection of 10,000,000 was given when the trypanosomes were increasing, and that rise was the highest recorded. This treatment was then stopped for some time.

It seems that the effect of these so-called vaccines, if injected immediately after the natural fall of the parasites, is a reproductive stimulation of the parasites, causing the next rise to occur sooner than was natural; and this premature rise tends to be less high than it probably should have been in the natural course of events. If, however, the vaccine be injected during the natural rise of the trypanosomes, it stimulates their reproduction, causing a very high and rapid rise, and the subsequent fall is also very sudden.

We confirmed these surmises later. On May 17 an injection of 30,000,000 dead trypanosomes was given, with the result that the following rise was completed on the sixth day.

Another injection of 50,000,000 on May 30 was followed by a rise at the normal time. A large dose of 100,000,000, injected on June 4, however, scarcely allowed the parasites any time to diminish, so that they completed their next rise on the fifth day, followed by

a sudden fall. Thus it would seem that the normal period of seven days between the rises of parasites may be shortened to six, five, and even four days, by an injection of dead trypanosomes.

Doses of vaccine up to 100,000,000 seemed to cause no harm. On the contrary, during the period from the 7th to the 28th of April, when small doses were given, the temperature was more uniform, and more near to normal than it had ever been before or after.

Again, from the 14th to the 19th of May, the patient was extremely ill, almost comatose, with a high temperature, and like to die. On May 17 he had vaccine (30,000,000), followed on May 19 by an injection of 10 c.c. of leucocytic extract. The improvement on May 20 was remarkable, both mentally and physically. Of course, at that time he had atoxyl and nuclein to increase the leucocytes, hence it is almost impossible to tell which was the potent factor. Against atoxyl having caused this good result, we may point out that it had no such effect either before or since.

As already stated, this marked improvement was coincident with a large increase of mononuclear leucocytes. We tried again to repeat this success by injecting vaccine (100,000,000 trypanosomes) on June 4, three days before the height of the parasitic rise, and leucocytic extract at the height of the rise, but the result was not so good. (*Vide* paper by Ross and J. G. Thomson.†)

IX. THE EFFECT OF SUBCUTANEOUS INJECTIONS OF LEUCOCYTIC EXTRACT

Thinking that the fall in the number of leucocytes might be a factor in the rise of trypanosomes, we determined to keep up the numbers of leucocytes when they were falling. Consequently, we tried an injection of nuclein (25 min.), but this did not seem to cause much increase of leucocytes. Yeast, 15 grains daily (by mouth), was also tried. It seemed to cause some increase, but not marked.

At this time Dr. Moore Alexander, pathologist to the hospital, suggested that we should try leucocytic extract. He thought that this extract might contain certain substances which would be deleterious to the trypanosomes, or which would neutralise their

† Proc. Roy. Soc., Vol. LXXXIII, 1911, p. 227.

endotoxins. He was good enough to prepare it for us by injecting Mellin's food into the pleural cavities of rabbits. The rabbits were then killed, and the accumulation of leucocytes taken from the pleural cavity, and extracted with sterile distilled water.

To our surprise, the effect of an injection of this leucocytic extract was to produce a very great increase of leucocytes in the blood on the day following the injection. This was almost the invariable result. In our opinion, it seems to be a far more powerful promoter of leucocyte increase than yeast or nuclein.

We tried to utilise this discovery in two ways:—

(i) To help the natural leucocyte increase by injecting the extract just at the height of the trypanosome rise. We did this on May 19. Next day, as we have mentioned, the patient showed a remarkable improvement. We were unable, however, to get such a happy result again.

(ii) By injecting the extract a day or two before the rise of parasites, we thought we might prevent that rise by causing an early increase in the leucocytes.

On May 31 10 c.c. of the extract were injected, producing next day an increase of leucocytes up to 20,000 per cubic millimetre of blood, but they diminished next day to 2,800 per cubic millimetre, and the increase of trypanosomes occurred all the same.

Later, just before the patient's death, we tried the effect of 1 c.c. doses of the extract daily. This seemed to keep the leucocyte count high, but unfortunately the results were complicated by the patient developing an abscess at this time, and later by the development of pleuro-pneumonia.

Further investigation with this substance, and with vaccine, would require to be made before coming to any definite conclusions. Such an investigation we think would lead to further knowledge regarding the natural balance of immunity between the body and the parasites.

It appears to be a law (at least it seems to hold good, we think, with leucocytes and trypanosomes) that the extract of dead animal cells stimulates the corresponding live cells to increase in numbers. This would appear to support the hypothesis put forward by Dr. H. C. Ross, that the extracts of dead tissues promote the proliferation of living cells.*

* Brit. Med. Journ., June 11, 1910.

X. CONCLUSIONS REGARDING THE NATURE AND CAUSE OF THE TRYPANOSOME CYCLE

The true explanation of this phenomenon must be of extreme importance, not only as regards the treatment of this disease, but also, we think, with regard to the problems of immunity in general.

Before stating our views we cannot do better than quote the following extract from the 'Sleeping Sickness Bulletin,' 1909, No. 12, p. 485:—

'*Des Causes des Crises Trypanolytic et des Rechûtes qui les suivent.* 'A MASSAGLIA. "Comptes Rendus de l'Academie des 'Sciences," Octobre, 1907.

'In some species of animals there are no crises. The 'trypanosomes increase in a progressive regular manner. In others 'the trypanosomes, after an increase, suddenly diminish to such an extent sometimes that they cannot be found in the blood. They 'soon reappear. Massaglia endeavoured to find out the cause of 'the crisis and the subsequent relapses. . . . *Conclusions:* 'Trypanolytic crises are due to the formation of anti-bodies in the 'blood. A few parasites escape destruction, because they become 'used or habituated to the action of these anti-bodies. These are 'the parasites which cause the relapses. Since the trypanosomes 'become more and more used to the anti-bodies the subsequent 'crises become less marked. . . . Thiroux's suggestion of a 'balance between anti-bodies and parasites is an interesting one 'and has some facts in its support. It would serve to explain the 'cause of real or apparent cures mentioned in Bulletin No. 5, 'pp. 193 and 195.'

Here it is clear that Massaglia has observed and has tried to explain the occurrence of these natural rises and falls of trypanosomes. Our opinions on the subject are as follows:—

(i) *The cycle is not due to an unconditional cyclical development of the parasites as is the case in malarial fever.*—If it were so then one would expect the cycle to be more regular, and one would not expect its time to be altered by vaccine injections. The time between the rises varies not only in the same individual, but in different animals. This would appear to suggest that the cycle is not due to a definite parasitic development as in malaria, but is

merely a question of a struggle between the defensive powers of the infected body and the aggressive powers of the trypanosomes.

The more susceptible the animal the shorter is the period between the rises as seen in the case of rats, in which the cycle is almost lost. Massaglia evidently failed to observe the slight remissions in the rat.

The greater the resistance of the infected animal the longer is the cyclical period, as in guinea-pig and man.

By an 'unconditional cycle' we mean one of which the *period* is not affected by the resistance of the host or by therapeutic agents—as, for instance, that of *Plasmodium*. By a 'conditional cycle' we mean one which is so affected—as in the present case.

(ii) *The increase of parasites is due to their sudden and active multiplication.*—The presence of numerous dividing forms during the cyclical rise would seem to support this statement.

(iii) *The multiplication of trypanosomes is extremely rapid.*—As before stated they seem capable of dividing in man three to four times in twenty-four hours.

In rats the rate of multiplication would seem much greater, as many as ten divisions or generations may occur in twenty-four hours.

(iv) *The rate of multiplication depends on the suitability of the infected blood to the parasite.*—The blood of rats seems more suitable to the parasite than the blood of man and guinea-pigs.

Also this suitability would appear to vary from time to time in the same animal. In our case there occurred high and low rises in the numbers of trypanosomes. Moreover the three highest rises recorded in the chart were followed by the three lowest rises recorded. This is a very significant fact. It would appear to indicate that a high rise sets up some reactionary condition. This reaction, if great, not only causes the decrease of trypanosomes but extends its influence so far as to reduce the next rise.

(v) *The fall in number of parasites is not due to the toxins they develop.*—In man the numbers may reach only 200 per cubic millimetre of blood and then they diminish, whereas in rats they may reach over 200,000 per cubic millimetre of blood and yet continue to rise, and the toxins in the latter case must be much more abundant than in the former.

It would seem, therefore, that the explanation may be reduced to some of the following causes, all of which may come into play.

(i) *The increase of trypanosomes is due to their active multiplication*, the rate of multiplication depending on the following conditions:—

(*a*) The liberation of a reproductive stimulant from the dead trypanosomes of the previous fall.

(*b*) The small number of leucocytes, especially mononuclears.

(*c*) The habituation of the trypanosomes to their anti-bodies.

(*d*) The absence or the diminution of anti-bodies to the trypanosomes.

(ii) *The decrease of trypanosomes is due to their rapid death and to a cessation of multiplication*, probably depending on the following conditions:—

(*a*) The presence of anti-bodies in the serum.

(*b*) The large increase of leucocytes, especially mononuclears.

(iii) *The trypanosomes remaining between the rises are resistant forms*, and tend to become spherical, especially in the internal organs. (*Vide* H. B. Fantham.*)

These resistant spherical forms also occur after atoxyl treatment (Moore and Breinl).

N.B.—The reference to the virulence of this trypanosome and to the cycle in rats and guinea-pigs is taken from the paper on enumerative studies in rats, guinea-pigs, and rabbits by H. B. Fantham and J. G. Thomson.†

The virulence of this strain was also noticed by L. E. W. Bevan and Malcolm Macgregor ('Journal of Comparative Pathology and Therapeutics,' June, 1910), who inoculated animals from our patient before he left N.E. Rhodesia.

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* Ann. Trop. Med. and Parasit., Vol. IV, pp. 465-485; also Proc. Roy. Soc., B, Vol. LXXXIII, pp. 212-227.

† Ann. Trop. Med. and Parasit., Vol. IV, pp. 417-463; also Proc. Roy. Soc., B, Vol. LXXXIII, pp. 206-211.

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TABLE OF DAILY DETAILS

W.A.—*Sleeping Sickness.* Infected September, 1909; admitted December, 1909; age 26; male; weight 154 lbs.; died June 29, 1910

NOTE.—The parasites are given per c.mm. The temperatures are recorded in the Haematothermic Fahrenheit scale, which is the Fahrenheit scale minus 95·0 multiplied by 10. The leucocytes are given in 100's per c.mm.; and the haemoglobin in Tallqvist's scale.

	February													March		
Date	16	17	18	19	20	21	22	23	24	25	26	27	28	1	2	3
Number of Tryps. per c.mm....	—	166	195	140	296	687	800	500	254	130	70	—	124	570	606	70
Maximum temp., H.F.	60	74	60	40	58	56	54	50	30	40	56	52	56	42	54	36
Average daily temp., H.F. ...	49	57	46	35	39	44	39	31	29	27	35	28	35	37	35	29
Total Leucocytes, in 100's ...	56	44	39	50	53	—	—	—	62	—	—	—	99	—	119	—
Polymorphs, in 100's	34	26	26	—	—	—	—	—	36	—	—	—	53	—	66	—
Mononuclears, in 100's	22	18	13	—	—	—	—	—	26	—	—	—	46	—	53	—
Mononuclears, per cent.	39	44	36	—	—	—	—	—	42	—	—	—	47	—	45	—
Hb. per cent. (Tallqvist)	R.B.C., 3,800,000	—	—	—	—	—	—	—	—	—	—	—	—	—	R.B.C., 3,800,000	—
Treatment	Atoxyl, 2 gr.	—	—	$HgCl_2$, $\frac{1}{5}$ gr.	—	Quinine, 30 gr. Meth. blue, 50 c.c.	*et seq.*		—	—	—	—	—	—	—	—

	March															
Date	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Number of Tryps. per c.mm.	26?	12	40	204	1256	1400	472	152	32	76	160	220	320	68	180	132
Maximum temp., H.F.	34	38	36	50	46	34	38	38	36	34	44	46	38	42	40	36
Average daily temp., H.F.	24	24	25	33	33	28	19	27	25	22	32	33	30	29	32	27
Total Leucocytes, in 100's	—	—	—	—	—	—	—	—	156	—	—	—	31	47	—	73
Polymorphs, in 100's	—	—	—	—	81	—	—	—	113	—	—	—	17	24	—	43
Mononuclears, in 100's	—	—	—	—	35	—	—	—	43	—	—	—	14	23	—	30
Mononuclears, per cent.	—	—	—	—	—	—	—	—	34	—	—	—	46	49	—	41
Hb. per cent. (Tallqvist)	—	—	85	85	80	—	—	—	80	—	85	85	80	75	80	82
Treatment	—	—	—	—	—	—	—	—	Quinine stopped	—	—	—	—	Tryp. red, 5 gr. $HgCl_2$, $\frac{1}{5}$ gr.	Tryp. red, 15 gr.	Tryp. red, 15 gr.

	March												April			
Date	20	21	22	23	24	25	26	27	28	29	30	31	1	2	3	4
Number of Tryps. per c.mm.	32	24	100	620	1136	322	68	72	32	188	748	1016	144	52	52	40
Maximum temp., H.F.	32	32	40	52	44	38	32	38	28	46	50	42	60	48	32	32
Average daily temp., H.F.	27	21	31	40	37	29	26	24	23	31	37	30	31	35	19	25
Total Leucocytes, in 100's	—	62	—	45	73	99	83	56	80	47	41	100	47	81	53	76
Polymorphs, in 100's	—	38	—	29	28	57	34	23	47	25	16	?	21	36	21	37
Mononuclears, in 100's	—	24	—	16	45	42	49	33	33	22	25	?	26	45	32	39
Mononuclears, per cent.	—	40	—	35	62	43	60	59	41	46	62	?	55	56	60	51
Hb. per cent. (Tallqvist)	85	85	85	82	85	85	85	—	85	85	85	80	80	80	80	80
Treatment	—	—	—	Trypsin, amylopsin	*et seq.*	—	Vaccine, 1,000,000	—	—	—	Quinine, 20 gr.	*et seq.* Izal oil, 8 min.	Izal oil, 8 min.	Izal oil, 8 min.	—	—

Date	April 5	6	7	8	9	10	11	12	13	14	15	16	17	18
Number of Tryps. per c.mm....	212	680	1164	340	116	172	416	556	650	192	96	172	116	392
Maximum temp., H.F.	52	46	40	34	32	30	40	40	40	30	30	38	40	40
Average daily temp., H.F. ...	37	28	27	23	19	21	33	26	25	21	25	25	24	31
Total Leucocytes, in 100's ...	61	56	89	59	84	53	40	70	62	81	52	?	—	—
Polymorphs, in 100's	33	34	44	35	59	22	19	45	—	41	32	?	—	—
Mononuclears, in 100's	28	22	44	24	25	31	21	25	—	40	20	?	—	—
Mononuclears, per cent.	46	40	50	41	30	58	53	36	—	49	39	47	49	48
Hb. per cent. (Tallqvist)	85	85	85	80	80	80	80	80	85	85	85	85	—	85
Treatment	Atoxyl, 4 gr.	—	—	—	Vaccine, 9,000,000	—	—	—	Succ. Hg, $\frac{1}{5}$ gr.	Atoxyl, 2 gr.	Atoxyl, 2 gr. Vaccine, 2,000,000	—	—	Succ. Hg, $\frac{1}{5}$ gr.

Date	April 19	20	21	22	23	24	25	26	27	28	29	30
Number of Tryps. per c.mm....	336	90	72	244	156	164	88	48	140	200	1536	120
Maximum temp., H.F.	36	32	52	44	34	32	38	38	32	32	52	42
Average daily temp., H.F. ...	23	22	31	34	27	24	27	27	24	25	32	30
Total Leucocytes, in 100's ...	100	—	—	—	100	130	100	72	120	240	108	140
Polymorphs, in 100's	52	—	—	—	60	78	70	—	64	144	52	66
Mononuclears, in 100's	48	—	—	—	40	52	30	—	56	96	56	74
Mononuclears, per cent.	48	36	31	52	40	40	30	—	46	40	52	53
Hb. per cent. (Tallqvist)	85	—	80	85	80	80	80	80	85	80	85	—
Treatment	—	Quinine stopped. Vaccine, 40,000,000	—	—	Vaccine, 10,000,000	—	Vaccine, 10,000,000	—	—	Vaccine, 10,000,000	—	Succ. Hg, $\frac{1}{5}$ gr.

	May										
Date	1	2	3	4	5	6	7	8	9	10	11
Number of Tryps. per c.mm.	64	64	68	76	292	8	40	108	56	64	8
Maximum temp., H.F.	38	34	40	48	44	46	46	34	54	44	46
Average daily temp., H.F.	24	28	30	34	32	24	27	26	35	25	31
Total Leucocytes, in 100's	500	110	53	73	210	174	230	350	150	75	62
Polymorphs, in 100's	265	70	33	40	101	87	138	168	63	25	25
Mononuclears, in 100's	235	40	20	33	109	87	92	182	87	50	37
Mononuclears, per cent.	47	36	38	45	52	50	40	52	58	66	59
Hb. per cent. (Tallqvist)	85	80	80	80	80	80	80	80	80	80	80
Treatment	—	Atoxyl, 2 gr.	Succ. Hg, $\frac{1}{5}$ gr.	—	Succ. Hg, $\frac{1}{5}$ gr. Atoxyl, 2 gr.	—	Succ. Hg, $\frac{1}{5}$ gr.	—	Succ. Hg, $\frac{1}{5}$ gr. Quin. et Meth. blue.	—	—

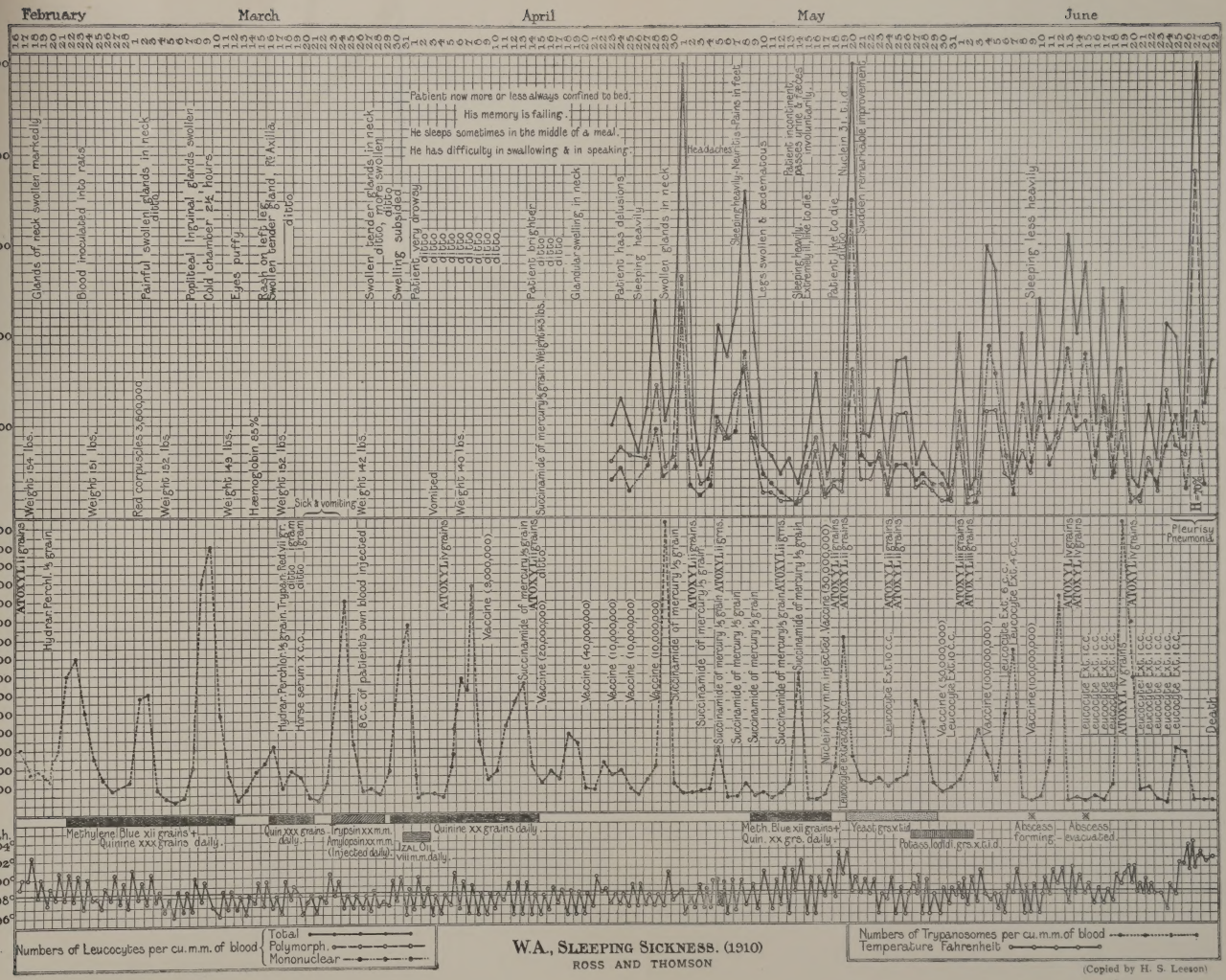
	May									
Date	12	13	14	15	16	17	18	19	20	21
Number of Tryps. per c.mm.	76	100	700	8	4	52	176	900	208	104
Maximum temp., H.F.	56	56	68	48	48	56	70	78	64	42
Average daily temp., H.F.	38	36	48	30	34	41	47	64	45	35
Total Leucocytes, in 100's	45	63	37	75	157	36	72	68	500	100
Polymorphs, in 100's	16	—	33	21	71	18	33	29	160	38
Mononuclears, in 100's	29	—	33	54	86	18	39	39	340	62
Mononuclears, per cent.	64	—	50	72	55	49	54	57	68	62
Hb. per cent. (Tallqvist)	80	75	80	80	80	80	80	80	80	85
Treatment	Succ. Hg, $\frac{1}{5}$ gr. Atoxyl, 2 gr.	—	Succ. Hg. $\frac{1}{5}$ gr.	—	—	Vaccine, 30,000,000 Nuclein, 25 min.	Atoxyl, 2 gr.	Atoxyl, 2 gr. Leuc. ext., 10 c.c.	—	—

	May										June
Date	22	23	24	25	26	27	28	29	30	31	1
Number of Tryps. per c.mm.	104	112	68	120	150	552	416	100	48	72	128
Maximum temp., H.F.	42	42	44	36	30	50	42	34	36	36	44
Average daily temp., H.F.	36	28	31	23	24	38	27	27	25	27	34
Total Leucocytes, in 100's	96	140	53	170	175	54	80	57	43	30	200
Polymorphs, in 100's	39	71	30	114	117	21	34	26	12	13	116
Mononuclears, in 100's	57	69	23	56	58	33	46	31	31	17	84
Mononuclears, per cent.	59	49	44	33	33	62	58	55	72	56	42
Hb. per cent. (Tallqvist)	85	—	85	85	85	85	85	85	80	80	80
Treatment	—	—	Atoxyl, 2 gr. Leuc. ext., 10 c.c.	Atoxyl, 2 gr.	—	—	—	—	Vaccine, 50,000,000	Leuc. ext., 10 c.c.	Atoxyl, 3 gr.

	June										
Date	2	3	4	5	6	7	8	9	10	11	12
Number of Tryps. per c.mm.	240	352	248	112	468	820	20	12	24	208	1164
Maximum temp., H.F.	44	56	54	30	38	56	40	40	46	56	58
Average daily temp., H.F.	34	33	36	21	24	39	27	26	30	41	48
Total Leucocytes, in 100's	28	40	300	270	110	45	200	80	240	108	160
Polymorphs, in 100's	14	23	114	119	45	27	72	33	130	49	74
Mononuclears, in 100's	14	17	186	151	65	18	128	47	110	59	86
Mononuclears, per cent.	50	43	62	56	59	40	64	59	46	55	54
Hb. per cent. (Tallqvist)	80	80	80	80	80	80	80	80	80	80	80
Treatment	Atoxyl, 3 gr.	—	Vaccine, 100,000,000	—	Leuc. ext., 4 c.c.	Leuc. ext., 4 c.c.	—	Vaccine, 100,000,000	—	—	—

	June							
Date	13	14	15	16	17	18	19	20
Number of Tryps. per c.mm....	16	32	8	32	16	100	1452	680
Maximum temp., H.F.	60	58	50	38	38	50	50	60
Average daily temp., H.F. ...	48	41	40	27	28	37	44	45
Total Leucocytes, in 100's ...	310	200	280	100	250	81	250	37
Polymorphs, in 100's	124	92	101	40	125	39	90	29
Mononuclears, in 100's	186	108	179	60	125	42	160	16
Mononuclears, per cent.	60	54	64	60	50	52	64	43
Hb. per cent. (Tallqvist)	80	80	—	—	80	—	80	80
Treatment	Atoxyl, 4 gr.	Atoxyl, 4 gr.	Leuc. ext., 1 c.c.	Leuc. ext., 1 c.c.	Leuc. ext., 1 c.c.	Leuc. ext., 1 c.c.	Atoxyl, 4 gr.	Atoxyl, 4 gr.

	June								
Date	21	22	23	24	25	26	27	28	29
Number of Tryps. per c.mm....	56	72	40	24	300	260	40	40	30
Maximum temp., H.F.	42	42	34	40	66	88	78	74	70
Average daily temp., H.F. ...	35	34	30	27	42	75	70	69	70
Total Leucoctes in 100's	32	120	60	210	195	84	500	126	—
Polymorphs, in 100's	13	61	28	147	78	66	380	105	—
Mononuclears, in 100's	19	59	32	63	117	18	120	21	—
Mononuclears, per cent.	60	49	54	35	60	21	24	17	—
Hb. per cent. (Tallqvist)	80	70	70	70	75	70	70	70	—
Treatment	Leuc. ext., 1 c.c.	Leuc. ext., 1 c.c.	Leuc. ext., 1 c.c.	Leuc. ext., 1 c.c.	Leuc. ext., 1 c.c.	—	—	—	—



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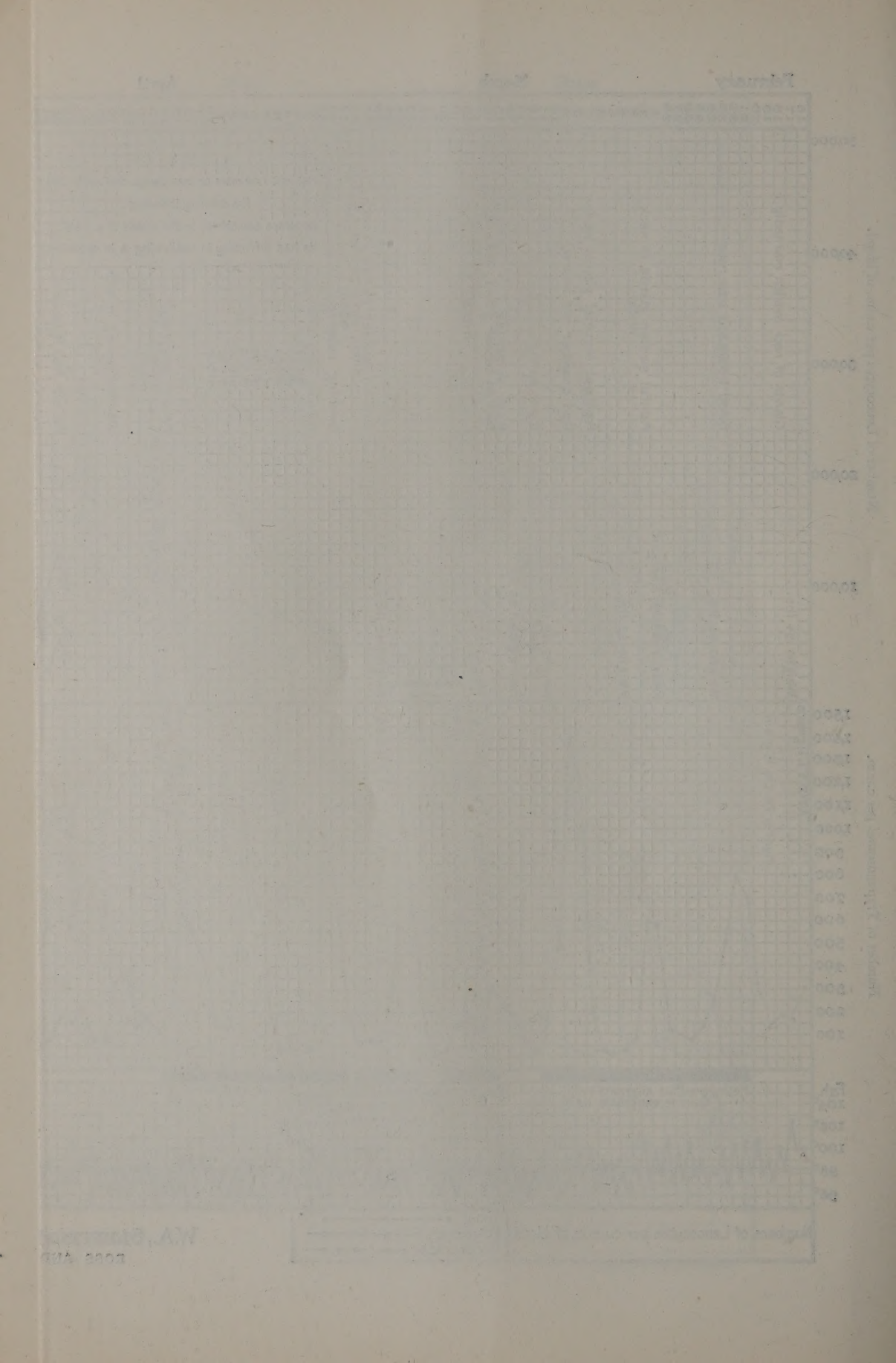

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